## Direct Access to Benzo[b]furans through Palladium-Catalyzed Oxidative Annulation of Phenols and Unactivated Internal Alkynes\*\*

Malleswara Rao Kuram, M. Bhanuchandra, and Akhila K. Sahoo\*

The ubiquitous benzo[*b*]furan is a privileged structure found in numerous natural products<sup>[1]</sup> and biologically active compounds.<sup>[2]</sup> Highly substituted benzo[*b*]furan motifs are also present in various drug leads<sup>[2]</sup> and organic materials.<sup>[3]</sup> As a result, there is considerable interest from the synthetic organic community to access the benzo[*b*]furan motif by efficient methodologies,<sup>[4]</sup> and indeed, various synthetically viable strategies have been devised for the construction of benzo[*b*]furan and its derivatives. Some of the conceptually most interesting synthetic strategies toward benzo[*b*]furans are shown in Scheme 1.<sup>[5]</sup>



Scheme 1. Strategies toward benzo[b]furans.

The typical method for the synthesis of oxygen-bearing heterocycles involves Lewis acid (LA) catalyzed condensation of phenol or halogenated arenes with ketones or aldehydes (path a, Scheme 1).<sup>[6]</sup> The Fe-catalyzed oxidative Pechmann-type condensation of phenols with  $\beta$ -keto esters is a notable strategy, enabling the single-step synthesis of polybenzofurans.<sup>[7]</sup> Unfortunately, this method does not give access to 2,3-diarylbenzo[*b*]furans. The transition-metal (TM)-catalyzed oxidative cyclization of *ortho*-disubstituted arene precursors, such as 1,2-dihaloarenes, *o*-hydroxybenzophenones, and *o*-bromobenzylbromides with ketones or aldehydes also furnishes benzo[*b*]furans (paths a and c, Scheme 1),<sup>[6]</sup> while regioselective cyclization of *o*-alkynylphenols and *o*-allylphenols readily gives 2- and/or 3-substituted

[*]	M R Kuram M Bhanuchandra Dr A K Sahoo
11	School of Chemistry University of Hyderabad
	School of Chemistry, Oniversity of Fryderadad
	Hyderadad (India)
	E-mail: akhilchemistry12@gmail.com
	akssc@uohyd.ernet.in
	Homepage: http://chemistry.uohyd.ernet.in/~aks/
[**]	We thank the CSIR. INDIA. the University of Hyderabad.

[\*\*] We thank the CSIR, INDIA, the University of Hyderabad, and ACRHEM for financial support. M.R.K. and M.B. thank CSIR, India for fellowship. Support of R. Kishore, C. C. Gupta, and Dr. P. Raghavaiah for the X-ray crystallographic analysis is appreciated.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210217.

benzo[b]furans (path b, Scheme 1).<sup>[8]</sup> A recent report demonstrated the synthesis of 2-methyl-3-aryl-benzofurans through Zn(OTf)2-catalyzed coupling and cyclization of phenols with terminal propargyl alcohols.<sup>[9]</sup> Larock et al. and other research groups demonstrated an elegant approach to benzo[b]furans, which involved the Pd-catalyzed intermolecular cyclization of ortho-halogenated phenols with unactivated alkynes (path d, Scheme 1).<sup>[10]</sup> The sigmatropic rearrangement of aryl oxime ethers,<sup>[11a]</sup> [3+2] cycloaddition of hydroquinones with enol ethers,<sup>[11b]</sup> and Ir-catalyzed cyclodehydration of  $\alpha$ -aryloxy ketones<sup>[11c]</sup> are a few noteworthy approaches that have been developed subsequently and expand the synthetic versatility of the oxidative cyclization protocol. Unfortunately, the synthetic potential of this strategy is limited by the requirement of functionalized precursors, which can only be obtained through specialized protocols involving multistep procedures.<sup>[5]</sup>

The TM-catalyzed oxidative annulation of anilines, phenols, and thiols with activated or unactivated alkynes offers a unique platform for the atom-efficient formation of heterocycles in a limited number of steps.<sup>[12]</sup> The groups of Miura and Ackermann have independently demonstrated the synthesis of naphthopyrans by employing the Rh- and Rucatalyzed oxidative annulation between  $\alpha$ -naphthol and alkynes, respectively.<sup>[13]</sup> An interesting disclosure from Trost and co-workers describes the synthesis of coumarin involving the Pd-catalyzed annulation between phenols and alkynoates.<sup>[14]</sup> Recently, Yu and co-workers reported an intramolecular C-H activation/C-O cyclization method toward dihydrobenzofurans directed by aliphatic alcohols.<sup>[15]</sup> An efficient approach to dibenzofurans is realized through intramolecular phenol-directed C-H activation/C-O cyclization protocols.<sup>[16]</sup> The Ru-catalyzed dehydrative ortho-C-H alkenylation and cyclization of phenols with 1,2-diols is a direct route to benzofurans recently disclosed by Yi and co-workers.<sup>[17]</sup>

While the TM-catalyzed annulation between aniline and unactivated alkynes provides indole and its derivatives with ease,<sup>[12]</sup> a detailed survey of the literature reveals that the one-step synthesis of benzofurans from readily available phenols and unactivated alkynes has so far remained elusive (path e, Scheme 1). The reactivity of phenol toward unactivated alkynes presents the following challenges: 1) the participation of an unfavorable four-membered oxygen-containing metallacycle,<sup>[18]</sup> 2) difficulties associated with the formation of the C–O bond through reductive elimination of the putative Pd<sup>II</sup> intermediates,<sup>[19]</sup> and 3) sensitivity of phenols to strong oxidants, which undergo homocoupling in the presence of TMs.<sup>[16a,20]</sup> Despite these cumulative challenges, herein we report the development of an unprecedented one-step synthesis of benzo[*b*]furans by the Pd-catalyzed oxidative



annulation of readily accessible phenols and unactivated internal alkynes.

We started the investigation by reacting 4-nitrophenol (1a) with diphenylacetylene (2a) in the presence of different combinations of palladium catalysts and phosphine ligands. In the presence of Pd(OAc)<sub>2</sub>, JohnPhos (L1) or dppe (L2) as ligands, K<sub>2</sub>CO<sub>3</sub> or Ag<sub>2</sub>CO<sub>3</sub> as bases, and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O as oxidant in 1,4-dioxane, no reaction occurred or dimerization of the phenol and/or alkyne was observed (entries 1 and 2).<sup>[21]</sup> To our delight, the desired product **3a** was formed in 40% yield (GC analysis) under the catalytic conditions comprising of [Pd<sub>2</sub>(dba)<sub>3</sub>], bathophenanthroline (L3), Ag<sub>2</sub>CO<sub>3</sub>, and AgOAc in dioxane (entry 3). Interestingly, the use of Cu- $(OAc)_2 H_2O$  as oxidant and  $Ag_2CO_3$  as base led to **3a** with an enhanced yield (entry 4). Among the range of Pd<sup>0</sup> catalysts and solvents that were surveyed, [Pd<sub>2</sub>(dba)<sub>3</sub>] and 1,4-dioxane appeared to be optimal.<sup>[21]</sup> An extensive screening of various combinations of catalysts, bases, and oxidants led to effective catalytic conditions (conditions A: [Pd<sub>2</sub>(dba)<sub>3</sub>], L3, AgOAc, and  $Cu(OAc)_2 \cdot H_2O$ , and **3a** was isolated in 92% yield (entry 5). Examination of other bidented ligands showed that the 1,10-phenanthroline (L4) was equally efficient (entry 6), while bathocuproine (L5) and 2,2'-bipyridyl (L6) produced trace amounts of **3a** (entries 7 and 8). These results show that the Pd<sup>0</sup> catalysts and the N-bearing bidented ligands are pivotal to this transformation and 3a was not produced in the absence of either  $[Pd_2(dba)_3]$  or L3.<sup>[21]</sup>

We recently demonstrated the hydrophenoxylation of phenols with alkynes for the synthesis of arylvinyl ethers.<sup>[22]</sup> A suitable combination of base and solvent was essential for this reaction to proceed, and we speculated that the acidity of the phenol is crucial.<sup>[22]</sup> Therefore, we studied the reaction between the electron-rich 4-methoxyphenol (1b) and 2a under optimized conditions (entry 5, Table 1). Unfortunately, only a trace of the desired benzofuran 3b was formed (GC analysis; entry 9). Thus, various combinations of bases, catalysts, ligands, and solvents were screened to find acceptable catalytic conditions for the synthesis of 3b (see the Supporting Information, Table S5).<sup>[21]</sup> Among the bases examined, NaOAc was the most suitable (entry 10). The yield of **3b** was marginally enhanced to 25% when L4 was employed (entry 11). Interestingly, performing the reaction with 4.0 equivalents of phenol afforded 3b in 40% yield (entry 12). Notably, an increased amount of 4-methoxyphenol (5.0 equiv) with respect to **2a** (1.0 equiv) significantly enhanced the efficiency of the reaction and produced 3b in 88% yield (entry 13, conditions B). The catalyst  $Pd(OAc)_2$ was found to be moderate (entry 14).

We next turned our attention to the scope and functionalgroup tolerance of this transformation. Scheme 2 summarizes the annulation of various phenols with **2a**. The nitrosubstituted benzofuran **3a** was obtained in excellent yield under conditions A in 24 h; in contrast, the known methods for the synthesis of **3a** involve multiple steps with overall poor yield.<sup>[23]</sup> The presence of a cyano group did not affect the reaction outcome, providing **3c** in 70% yield. Interestingly, ketone, aldehyde, and ester functionalities on the phenol were inert to the reaction conditions, and the desired products **3d–f** were isolated in good yields. Surprisingly, conditions B were Table 1: Optimization of the reaction conditions.[a]



[a] Reaction conditions: 1 (2.0 equiv), 2 (20 mg, 1.0 equiv, 0.11 mmol), catalyst (5 mol%), ligand (10 mol%), base (2.0 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (2.0 equiv), and 1,4-dioxane (2.0 mL) at 130 °C for 24–48 h. n.d. = not detected. [b] Conversion based on analysis of the crude by gas chromatography (GC) using dodecane as internal standard. [c] AgOAc was used as oxidant. [d] Yield of isolated product on 1.0 mmol scale. [e] 1b (4.0 equiv) and base (4.0 equiv) was used. [f] 1b (5.0 equiv) and base (5.0 equiv) was used. Entries in bold mark optimized reaction conditions.

superior over conditions A in the case of 4-hydroxybenzaldehyde (1e) and 4-hydroxymethylbenzoate (1 f); the reason for this observation is unclear. The halogen functionalities (F and Cl) were tolerated, and the reactions of 4-fluorophenol (1g) and 4-chlorophenol (1h) with 2a under conditions B delivered the desired benzofurans. X-ray crystallographic analysis confirms the structure of  $3g.^{\sc{[24]}}$  We studied the relative stability of common N- and O-protecting groups under the current catalytic conditions. Unfortunately, 4-aminophenol or N-methyl-4-aminophenol failed to react with 2a, whereas the annulation between N-acetyl-4-aminophenol and 2a proceeded smoothly under conditions B, and 3i was exclusively obtained, leaving the NHAc moiety untouched. We next envisaged the reaction of a hydroquinone with 2a, which would enlarge the molecular diversity; unfortunately, our efforts to incorporate multiple benzofurans on hydroquinone failed. Gratifyingly, the desired product 3j was obtained from the mono-O-benzoyl protected hydroquinone (1j) and 2a in good yield with the O-benzoate protecting group intact.

The electron-rich 4-methoxyphenol (1b) and 4-methylphenol (1k) were both reacted with 2a under conditions B to provide 3b and 3k in 88% and 70% yield, respectively. Remarkably, when *meta*-substituted phenols were annulated with 2a, highly regioselective benzofuran products 3l-n were produced through the formation of C–C bonds at the lesshindered side of the phenol (Scheme 2). As expected, the reaction of 2a with the structurally demanding *ortho*-sub-



**Scheme 2.** Substrate scope of phenols. Reaction conditions A: 1 (2.0 equiv), **2** (178 mg, 1.0 equiv, 1.0 mmol), [Pd<sub>2</sub>(dba)<sub>3</sub>] (5.0 mol%), **L3** (10 mol%), AgOAc (2.0 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (2.0 equiv), 1,4dioxane (8.0 mL) at 130°C; conditions B: **1** (5.0 equiv), **2** (178 mg, 1.0 equiv, 1.0 mmol), [Pd<sub>2</sub>(dba)<sub>3</sub>] (5.0 mol%), **L4** (10 mol%), NaOAc (5.0 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (2.0 equiv), 1,4-dioxane (8.0 mL) at 130°C.

stituted phenols 10 and 1p led to moderate amounts of the corresponding benzofurans 30 and 3p. On the other hand, the electron-neutral phenol (1q) reacted sluggishly with 2a under both optimized conditions and provided 3q in poor yield even with the extended reaction time. Pleasingly, heterocyclic, substituted phenol 1r efficiently annulated with 2a and afforded 3r in 91% yield.

Next, we examined the effect of electron-rich and electron-deficient aryl-substituted alkynes (Scheme 3). Annulation of the electron-poor 4-fluorophenol (**1g**) or the electron-rich 4-methoxyphenol (**1b**) with the electron-rich 4-methoxyphenyl-substituted alkyne **2b** produced the desired benzofurans **4a** and **4b** in 69% and 67% yields, respectively. Similarly, the electron-poor 4-chlorophenyl-substituted alkyne **2c** underwent annulation with **1b** efficiently. Under conditions B, 1,2-di(thiophen-2-yl)ethyne (**2d**) was efficiently reacted with **1a**, resulting in **4d** in 55% yield. Because of the lack of conjugation, the alkyl-substituted alkyne is less reactive.<sup>[25]</sup> Interestingly, the desired 2,3-dialkyl-substituted benzofuran **4e** was furnished from 4-chlorophenol (**1h**) and 4-octyne (**2e**) in 63% yield. The benzofuran products were



**Scheme 3.** Substrate scope of alkynes. Reaction conditions A and B summarized in Scheme 2.

formed with high regioselectivity when phenols and alkyl, aryl-substituted alkynes were reacted. Reaction of 4-nitrophenol (1a) with phenyl- and *n*-butyl-substituted alkyne 2f exclusively delivered 3-butyl-5-nitro-2-phenylbenzofuran (4f) in 81% yield. The structure of 4f was established based on NOESY studies and X-ray diffraction analysis.<sup>[24,26]</sup> The use of a bulky internal alkyne, such as 1-(hex-1ynyl)naphthalene (2g), did not affect the regioselectivity, giving 4g in 64 % yield.<sup>[26]</sup> Similarly, the desired regioselective product 4h was isolated in good yield from the reaction of meta-substituted 3-methoxyphenol (11) with 2 f.<sup>[26]</sup> To our delight, our results consistently agree with the observations of the groups of Larock<sup>[27]</sup> and Fagnou:<sup>[25a]</sup> the aryl moiety is incorporated adjacent to the oxygen functionality in benzofurans. Similarly, the annulation between the electron-rich 4methoxyphenol (1b) and 1-(hex-1-vnvl)-4-methoxybenzene (2h) proceeded smoothly and regioselectively produced the benzofuran product **4i** in good yield.<sup>[26]</sup> Unfortunately, terminal alkynes were incompatible and largely produced the corresponding alkyne homocoupling products.<sup>[25a]</sup>

Various complex phenol derivatives of pharmaceutical importance were examined to prove the synthetic potential of this strategy (Scheme 4).<sup>[28]</sup> The *N*-Boc-L-tyrosine methyl ester successfully underwent annulation with **2a** and gave the desired benzofuran derivative **3s** in 65% yield. Gratifyingly, the base-mediated reaction did not affect the stereointegrity of the L-tyrosine moiety, even at the elevated temperature. Despite its complex structure, estrone reacted with **2a** and afforded **3t** in good yield.<sup>[28d,24]</sup> A moderate amount of the desired benzofuran product **3u** was obtained from umbelliferone and **2a**, without affecting the lactone functionality of the coumarin moiety. Pleasingly, the *ortho*-substituted vanillylidenacetone, the chief constituent of the fragrant vanilla derivative,<sup>[28b]</sup> reacted sluggishly with **2a** to provide **3v** in poor yield.



Scheme 4. Derivatives of biologically important molecules.

When  $\alpha$ -naphthol (1w) was reacted with 2a under conditions B, the naphthofuran product 3w was exclusively isolated, albeit in poor yield, instead of the naphthopyran (Scheme 5).<sup>[13,21]</sup> Pleasingly, the desired naphthofuran 3x was obtained with an enhanced yield from the annulation between 1w and electron-rich alkyne 2b.<sup>[21]</sup> Similarly, the electronpoor alkyne 2c reacted with 1w under conditions B and delivered the napthofuran 3y in moderate yield.<sup>[21]</sup> Thus, two distinct products can be produced independently under Rh or Pd catalysis.



Scheme 5. Switching the site selectivity.

Although a precise reaction mechanism remains to be established, a plausible mechanism is outlined in Scheme 6. Even though a Pd<sup>0</sup> source was used under optimized reaction conditions, we assume that the reaction is initiated by a Pd<sup>II</sup> intermediate, as Pd<sup>0</sup> is readily oxidized to Pd<sup>II</sup> in the presence of Cu(OAc)<sub>2</sub>.<sup>[14]</sup> Thus, coordination of the N-bearing bidentate ligand to [Pd<sub>2</sub>(dba)<sub>3</sub>], followed by Cu(OAc)<sub>2</sub>-assisted oxidation of 5, generates the active Pd<sup>II</sup> species 6.<sup>[14]</sup> At this stage, attack of phenol onto the electrophilic Pd<sup>II</sup> species may occur in two different ways. Mechanistic cycle A (Scheme 6) involves the attack of phenol onto 6 to produce Pd<sup>II</sup>phenoxide species 7 and liberate AcOH.<sup>[29]</sup> Subsequently, the coordination of the alkyne to 7 would induce its phenoxypalladation to afford 8. Base-assisted intramolecular ortho-C-H insertion by the Pd catalyst then leads to 9.<sup>[30]</sup> Finally, reductive elimination delivers the benzofuran 3q and regenerates the Pd<sup>0</sup> species for the next catalytic cycle. On the other hand, mechanistic cycle B involves the ortho palladation of phenol by electrophilic Pd<sup>II</sup> species 6, giving the quinone-type intermediate 10.<sup>[14,31]</sup> Alkyne coordination followed by carbopalladation then affords 11, whereupon baseinduced rearomatization yields 12. The catalytic cycle is completed by the liberation of the product along with Pd<sup>0</sup> through reductive elimination of 12. A significant kinetic



Scheme 6. Proposed mechanistic cycle.

isotope effect was observed  $(K_{\rm H}/K_{\rm D} = 3.0)$  when a 1:1 mixture of phenol (**1q**) and [D<sub>5</sub>]phenol ([D<sub>5</sub>]-**1q**) was reacted with **2a**, thus supporting the participation of Pd-mediated C–H bond cleavage (cycle A).<sup>[21,30]</sup> Furthermore, as reported by van Koten and co-workers, bis(aryloxo)–Pd<sup>II</sup> complexes will form adducts with phenols through hydrogen bonding, a requirement for the completion of the reaction,<sup>[29]</sup> thus clearly supporting the need for an excess amount of phenol (see the Supporting Information).

Because the catalytic conditions of the benzofuran synthesis did not affect the NHAc moiety, we envisioned the installation of the indole and carbazole skeletons on molecular templates following known synthetic protocols. The procedure established by Fagnou and co-workers for the synthesis of indoles under Rh catalysis was applied, and the oxidative coupling between aniline precursor **3i** and **2a** was performed first. Gratifyingly, the three-ring-fused heterocycle **13** was isolated in 60 % yield (Scheme 7).<sup>[32a]</sup> The Pd-catalyzed anilide-directed arylation at the less-hindered *ortho*-C–H bond in **3i** with trimethoxyphenylsilane under the conditions developed by Shi and co-workers gave **14** in 75 % yield.<sup>[32b]</sup> Finally, Buchwald's intramolecular C–N arylation of **14** delivered novel four-ring-fused heteroaromatic compound **15** with ease (Scheme 7).<sup>[32c]</sup>

In summary, we have developed a novel one-step synthesis of 2,3-disubstituted benzofurans involving Pd-catalyzed oxidative annulations of commercially available phenols with



Scheme 7. Extending the molecular framework.

Angew. Chem. Int. Ed. 2013, 52, 4607-4612

readily accessible unactivated internal alkynes. The reaction exhibits a broad substrate scope. A single regioisomeric benzofuran was obtained with aryl,alkyl-substituted alkynes, whereas reaction of 1-naphthol with alkynes exclusively produced the naphthofurans rather than naphthopyrans. The inertness of the NHAc functional group in this benzofuran synthesis allows the creation of novel extended  $\pi$ conjugated heterocycles. Efforts are under way to develop milder reaction conditions and unravel mechanistic details.

Received: December 21, 2012 Revised: January 31, 2013 Published online: March 25, 2013

**Keywords:** alkynes · benzo[b]furans · oxidative annulation · phenols · regioselectivity

- For benzo[b]furan containing natural products, see: a) "Furans and Their Benzo Derivatives": D. M. X. Donelly, M. J. Meegan *Comprehensive Heterocyclic Chemistry, Vol. 4* (Ed.: A. R. Katritzky), Pergamon, New York, **1984**, pp. 657–712; b) P. Cagniant, D. Cagniant, *Adv. Heterocycl. Chem.* **1975**, *18*, 337.
- [2] For biological and pharmaceutical properties, see: a) X.-L. Hou, Z. Yang, H. N. C. Wong, *Progress in Heterocyclic Chemistry*, *Vol. 14* (Eds.: G. W. Gribble, T. L. Gilchrist), Elsevier, Oxford, UK, **2002**, p. 139; b) K. M. Zareba, *Drugs Today* **2006**, *42*, 75.
- [3] For benzo[b]furans in organic materials, see: a) B. Walker, A. B. Tamayo, X.-D. Dang, P. Zalar, J. H. Seo, A. Garcia, M. Tantiwiwat, T.-Q. Nguyen, Adv. Funct. Mater. 2009, 19, 3063;
  b) H. Tsuji, C. Mitsui, L. Ilies, Y. Sato, E. Nakamura, J. Am. Chem. Soc. 2007, 129, 11902.
- [4] For selected reviews on the synthesis of benzofurans, see: a) R. Chinchilla, C. Nájera, *Chem. Rev.* 2007, *107*, 874; b) G. Zeni, R. C. Larock, *Chem. Rev.* 2006, *106*, 4644; c) S. Cacchi, G. Fabrizi, A. Goggiamani, *Curr. Org. Chem.* 2006, *10*, 1423; d) R. E. Ziegert, J. Toräng, K. Knepper, S. Bräse, *J. Comb. Chem.* 2005, *7*, 147; e) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* 2004, *104*, 3079; f) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* 2003, *103*, 893.
- [5] For various strategies on the synthesis of 2,3-disubstituted benzofurans, see: a) A. Carrër, J.-C. Florent, E. Auvrouin, P. Rousselle, E. Bertounesque, J. Org. Chem. 2011, 76, 2502; b) L. M. Geary, P. G. Hultin, Eur. J. Org. Chem. 2010, 5563; c) A. R. Katritzky, Y. Ji, Y. Fang, I. Prakash, J. Org. Chem. 2001, 66, 5613, and references therein.
- [6] For selected examples, see: a) M. J. Moure, R. SanMartin, E. Dominguez, Angew. Chem. 2012, 124, 3274; Angew. Chem. Int. Ed. 2012, 51, 3220; b) F. Schevenels, I. E. Markó, Org. Lett. 2012, 14, 1298; c) L. Arias, Y. Vara, F. P. Cossío, J. Org. Chem. 2012, 77, 266; d) J. Bonnamour, M. Piedrafita, M. Bolm, Adv. Synth. Catal. 2010, 352, 1577; e) C. Eidamshaus, J. D. Burch, Org. Lett. 2008, 10, 4211; f) L. De Luca, G. Giacomelli, G. Nieddu, J. Comb. Chem. 2008, 10, 517; g) J. B. Wright, J. Org. Chem. 1960, 25, 1867; h) R. B. Adams, L. Whitaker, J. Am. Chem. Soc. 1956, 78, 658.
- [7] X. Guo, R. Yu, H. Li, Z. Li, J. Am. Chem. Soc. 2009, 131, 17387.
- [8] For selected examples, see: a) N. Matsuda, K. Hirano, K. Satoh, M. Miura, J. Org. Chem. 2012, 77, 617; b) C. Kanazawa, K. Goto, M. Tereda, Chem. Commun. 2009, 5248; c) C. Martínez, R. Álvarez, J. M. Aurrecoechea, Org. Lett. 2009, 11, 1083; d) Y. Liang, S. Tang, X.-D. Zhang, L.-Q. Mao, Y.-X. Xie, J.-H. Li, Org. Lett. 2006, 8, 3017; e) M. Nakamura, L. Ilies, S. Otsubo, E. Nakamura, Angew. Chem. 2006, 118, 958; Angew. Chem. Int. Ed. 2006, 45, 944; f) D. Yue, T. Yao, R. C. Larock, J. Org. Chem. 2005, 70, 10292; g) A. Fürstner, P. W. Davies, J. Am. Chem. Soc.

**2005**, *127*, 15024; h) I. Nakamura, Y. Mizushima, Y. Yamamoto, J. Am. Chem. Soc. **2005**, *127*, 15022; i) T. Yao, D. Yue, R. C. Larock, J. Org. Chem. **2005**, *70*, 9985; j) A. Arcadi, S. Cacchi, M. D. Rosario, G. Fabrizi, F. Marinelli, J. Org. Chem. **1996**, *61*, 9280, and references therein; for oxidative C–C/C–O cyclization, see: k) C. Li, Y. Zhang, P. Li, L. Wang, J. Org. Chem. **2011**, *76*, 4692; l) E. M. Ferreira, H. Zhang, B. M. Stoltz, *Tetrahedron* **2008**, *64*, 5987; m) S. W. Youn, J. I. Eom, Org. Lett. **2005**, *7*, 3355; n) H. Zhang, E. M. Ferreira, B. M. Stoltz, Angew. Chem. **2004**, *116*, 6270; Angew. Chem. Int. Ed. **2004**, *43*, 6144.

[9] M. P. Kumar, R.-S. Liu, J. Org. Chem. 2006, 71, 4951.

- [10] For selected examples, see: a) R. Wang, S. Mo, Y. Lu, Z. Shen, Adv. Synth. Catal. 2011, 353, 713; b) J.-R. Wang, K. Manabe, J. Org. Chem. 2010, 75, 5340; c) N. Sakai, N. Uchida, T. Konakahara, Tetrahedron Lett. 2008, 49, 3437; d) G. S. Gill, D. W. Grobelny, J. H. Chaplin, B. L. Flynn, J. Org. Chem. 2008, 73, 1131; e) R. Sanz, M. P. Castroviejo, Y. Fernández, F. J. Faňanás, J. Org. Chem. 2005, 70, 6548; f) R. C. Larock, E. K. Yum, M. J. Doty, K. K. C. Sham, J. Org. Chem. 1995, 60, 3270; g) A. Arcadi, F. Marinelli, S. Cacchi, Synthesis 1986, 749; h) C. E. Castro, E. J. Gaughan, D. C. Owsley, J. Org. Chem. 1966, 31, 4071.
- [11] a) N. Takeda, O. Miyata, T. Naito, *Eur. J. Org. Chem.* 2007, 1491;
  b) L. Alvey, S. Prado, V. Huteau, B. Saint-Joanis, S. Michel, M. Koch, S. T. Cole, F. Tillequin, Y. L. Janin, *Bioorg. Med. Chem.* 2008, *16*, 8264; c) K. Tsuchikama, Y.-k. Hashimoto, K. Endo, T. Shibata, *Adv. Synth. Catal.* 2009, *351*, 2850.
- [12] For selected recent reviews, see: a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* 2012, *41*, 3651; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* 2010, *110*, 624; c) T. Satoh, M. Miura, *Chem. Eur. J.* 2010, *16*, 11212.
- [13] a) S. Mochida, M. Shimizu, K. Hirano, T. Satoh, M. Miura, *Chem. Asian J.* **2010**, *5*, 847; b) V. S. Thirunavukkarasu, M. Donati, L. Ackermann, *Org. Lett.* **2012**, *14*, 3416.
- [14] B. M. Trost, F. D. Toste, K. Greenman, J. Am. Chem. Soc. 2003, 125, 4518.
- [15] X. Wang, Y. Lu, H.-X. Dai, J.-Q. Yu, J. Am. Chem. Soc. 2010, 132, 12203.
- [16] a) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu, L. Liu, J. Am. Chem. Soc. 2011, 133, 9250; b) Y. Wei, N. Yoshikai, Org. Lett. 2011, 13, 5504; c) J. Zhao, Y. Wang, Y. He, L. Liu, Q. Zhu, Org. Lett. 2012, 14, 1078; d) J. Zhu, Y. Wang, Q. Zhu, Synthesis 2012, 1551.
- [17] D.-H. Lee, K.-H. Kwon, C. S. Yi, J. Am. Chem. Soc. 2012, 134, 7325.
- [18] R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, Angew. Chem. 2003, 115, 116; Angew. Chem. Int. Ed. 2003, 42, 112.
- [19] a) D. Maiti, S. L. Buchwald, J. Am. Chem. Soc. 2009, 131, 17423;
  b) J. P. Stambuli, Z. Weng, C. D. Incarvito, J. F. Hartwig, Angew. Chem. 2007, 119, 7818; Angew. Chem. Int. Ed. 2007, 46, 7674;
  c) A. V. Vorogushin, X. Huang, S. L. Buchwald, J. Am. Chem. Soc. 2005, 127, 8146;
  d) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, J. Am. Chem. Soc. 1999, 121, 3224.
- [20] a) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang, M. C. Kozlowski, J. Org. Chem. 2003, 68, 5500; b) M. Smrčina, J. Poláková, Š. Vyskočil, P. Kočovský, J. Org. Chem. 1993, 58, 4534; c) A. S. Hay, H. S. Blanchard, G. F. Endres, J. W. Eustance, J. Am. Chem. Soc. 1959, 81, 6335; d) A. Wang, H. Jiang, Q. Xu, Synlett 2009, 929.
- [21] See the Supporting Information for more details.
- [22] M. R. Kuram, M. Bhanuchandra, A. K. Sahoo, J. Org. Chem. 2010, 75, 2247.
- [23] A. Bochicchio, L. Chiummiento, M. Funicello, M. T. Lopardo, P. Lupatelli, *Tetrahedron Lett.* 2010, 51, 2824.
- [24] See the Supporting Information for ORTEP diagrams. CCDC 916320 (3g), 916321 (3t), 916322 (4f) contain the supplementary crystallographic data for this paper. These data

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can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.

- [25] a) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, J. Am. Chem. Soc. 2010, 132, 18326; b) S. Rakshit, F. W. Patureau, F. Glorius, J. Am. Chem. Soc. 2010, 132, 9585.
- [26] NOESY studies confirm the structures of **4f-4i**. For further details see the Supporting Information.
- [27] R. C. Larock, E. K. Yum, M. D. Refvik, J. Org. Chem. 1998, 63, 7652.
- [28] a) M. Gynther, K. Laine, J. Ropponen, J. Leppänen, A. Mannila, T. Nevalainen, J. Savolainen, T. Järvinen, J. Rautio, J. Med. Chem. 2008, 51, 932; b) B. N. Shyamala, M. M. Naidu, G. Sulochanamma, P. Srinivas, J. Agric. Food Chem. 2007, 55, 7738; c) S. P. Pillai, S. R. Menon, L. A. Mitscher, C. A. Pillai,

D. M. Shankel, *J. Nat. Prod.* **1999**, *62*, 1358; d) N. M. Howarth, A. Purohit, M. J. Reed, B. V. L. Potter, *J. Med. Chem.* **1994**, *37*, 219.

- [29] G. M. Kapteijn, D. M. Grove, H. Kooijman, W. J. J. Smeets, A. L. Spek, G. van Koten, *Inorg. Chem.* **1996**, *35*, 526.
- [30] D. Lapointe, K. Fagnou, Chem. Lett. 2010, 39, 1118.
- [31] a) M. Ochiai, K. Fukui, S. Iwatsuki, K. Ishihara, K. Matsumoto, Organometallics 2005, 24, 5528.
- [32] a) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, J. Am. Chem. Soc. 2008, 130, 16474; b) S. Yang, B. Li, X. Wan, Z. Shi, J. Am. Chem. Soc. 2007, 129, 6066; c) W. C. P. Tsang, N. Zheng, S. L. Buchwald, J. Am. Chem. Soc. 2005, 127, 14560.